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Reprinted Article "Prospective Randomised Study of Endovenous Radiofrequency Obliteration (Closure) Versus Ligation and Vein Stripping (EVOLVeS): Two-year Follow-up"☆

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Quality of life

Abstract *Purpose:* To study intermediate clinical outcomes, rates of recurrent varicosities and neovascularisation, ultrasound changes of the GSV, and the quality of life changes in patients from EVOLVeS trial.
Methods: Forty five patients were re-examined 1 year and 65 two years after treatment. Follow-up visits included clinical examination with CEAP classification and calculation of venous clinical severity score (VCSS), ultrasound examination, and a quality of life questionnaire.
Results: The clinical course of the disease (CEAP, VCSS) was similar in the two treatment groups. 51% of the GSV trunks occluded by RFO underwent progressive shrinkage with the external diameter decreased from 6.3 SD 1.4 mm at 72 h after treatment to 2.9 SD 1.5 mm at 2 years. An additional 41% of the GSV became undetectable by ultrasound at 2-year follow up. In two patients we observed re-opening of an initially closed GSV lumen. Neovascularisation was found in one RFO case and in four S and L cases. Cumulative rates of recurrent varicose veins at combined 1 and 2 years follow-up were 14% for RFO and 21% for S and L (NS). The difference in global QOL score in favour of RFO re-appeared at 1 year and remained significant at 2 years after treatment.

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Conclusion: The 2-year clinical results of radiofrequency obliteration are at least equal to those after high ligation and stripping of the GSV. In the vast majority of RFO patients the GSV remained permanently closed, and underwent progressive shrinkage to eventual sonographic disappearance. Recurrence and neovascularisation rates were similar in the two groups although limited patient numbers prevent reliable statistical analysis. Improved quality of life scores persisted through the 2-year observations in the RFO group compared to the S and L group.

Introduction

Varicose veins is a common clinical problem which has a significant effect upon quality of life.[1] Reflux in the great saphenous vein (GSV) is one of the most frequent causes of primary chronic venous disease (CVD). This may progress to cause patient disability if left untreated.[2] The frequency of varicose veins, which is increasing as the average age of the population rises, makes this disease a significant public health issue.

High ligation and stripping of the GSV (S and L) has been found to be effective in the treatment of GSV incompetence. This operation directly addresses the problem of the incompetent GSV by removing it from the circulation. Although long-term results of surgical treatment show a high rate of recurrence,[3–11] S and L has become a standard of care for patients with GSV insufficiency. Morbidity associated with incisions and surgical removal of the vein, and temporary post-surgical decline in the quality of life, are the major drawbacks of S and L.[1,12] Attempts to minimise surgical trauma, and to preserve the GSV as a potential conduit by high ligation without removal of the vein, have been shown to lead to even higher recurrence rates.[3,13] Failure to ligate all proximal tributaries of the GSV is thought to be one of the major causes of recurrence after stripping and high ligation.[14] This concept has never been proven by an appropriately designed study.

The recently developed technology of endovascular obliteration of the GSV using temperature-controlled radiofrequency energy (Closure(r) procedure) is aimed at removing the vein from the circulation whilst minimising the consequences for the patient. A multi-centre randomised controlled trial (EVOLVeS) demonstrated the superiority of the Closure procedure compared to vein stripping in its impact on the quality of life, time of return to preoperative level of physical activity and time of return to work (RTW).[12] The original study design was limited to a 4-month period after surgery, and therefore did not address the question of mid- or long-term effect of the procedure and of recurrence rate.

Reports of non-randomised case series of Closure procedures demonstrated a low recurrence rate after 24 months.[15–17] Ultrasound follow-up to 2 years demonstrated that the GSV remains closed and that the proximal tributaries maintain their patency and competence.[16] These observations cannot be directly compared to reported results of vein stripping because of possible differences in patient population, surgical techniques and clinical settings. Follow-up of the patients enrolled in the EVOLVeS study can reveal important information on the durability of the Closure procedure, recurrence rates following both treatments, and duration of their effect on quality of life. This report presents results of 1 and 2-year clinical and ultrasound follow-up data and quality of life surveys in the patients enrolled in the EVOLVeS study.

Materials and Methods

A detailed description of the EVOLVeS protocol, patient selection criteria, and treatments has been published in our initial report.[12] Several important aspects of this study deserve mention here.

A total of 85 patients entered the study with 45 patients (46 limbs) allocated to radiofrequency obliteration (RFO) and 40 patients to high ligation and stripping (S and L), and 79 patients (80 limbs) received treatment (Fig. 1). Recruitment was terminated mainly due to reluctance on the part of patients to be blindly allocated to one or other of the treatment options. The treatment was randomly assigned via an internet based central system for all of the five participating sites (France-2, Austria-1, United States-2).

Each of the participating sites had obtained an approval of Institutional Review Board or Ethics committee of the institution. Patients gave their informed written consent for inclusion in the study.

Individuals with symptomatic varicose veins and incompetence of the great saphenous vein confirmed by duplex ultrasound examination who were candidates for conventional vein stripping were eligible for inclusion in the study.

During each patient's visit a standard set of information was collected. Physicians assessed patient's signs and

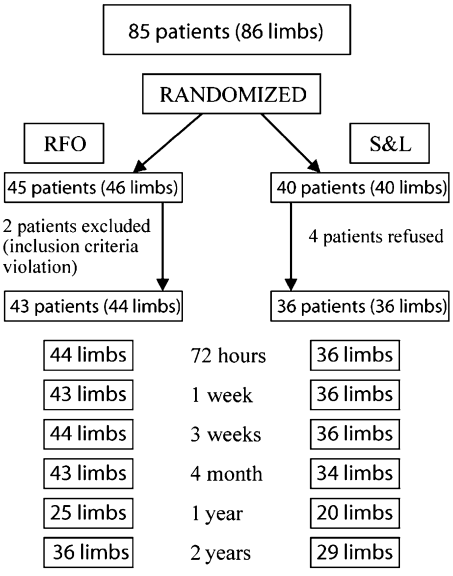

Figure 1 Study design.

symptoms utilising venous clinical severity score (VCSS),[18] and completed CEAP classification. They assessed patient's limbs for the presence of recurrent varicose veins. Ultrasound examination included measuring the external (adventitia-to-adventitia) and internal (intima-to-intima) diameters of the great saphenous vein (GSV) and characteristics of outflow and reflux. In addition, each patient completed the 20-question CIVIQ2 quality of life questionnaire that has been validated for use in patients with chronic venous disease.[19,20] In the analysis, each of the dimension scores, and the global scores, were transformed into a scale of 0-100.[19] Zero represents the least possible impact on daily activities and well being, i.e. highest quality of life, while 100 represents a maximum negative impact.

The only difference between the two groups was in treatment of the GSV. Both RFO and S and L were performed in the great saphenous vein from the knee, or upper calf, to the sapheno-femoral junction. Adjunctive procedures on varices and perforators were limited to below-the-knee sites in order to avoid confusion post-operatively between morbidity due to the saphenous vein treatment of the Closure procedure versus stripping and that due to the adjunctive procedure.

Post-operative visits were at 72 h, 1 week, 3 weeks, 4 months, 1 and 2 years (Fig. 1). At 1 and 2 years follow-up additional information was collected. The presence of neovascularisation in the groin was assessed by duplex ultrasound examination. This was defined as multiple small vessels in the groin reconnecting more proximal vein or its tributaries and the distal patent vein below the site of interruption (S and L) or occlusion (RFO). In cases where varicose veins were present, the question of whether varicosities were new or pre-existing was considered. New varicose veins below the knee were classified as recurrent varicosities. Special attention was paid to visualisation of the GSV after RFO to detect recanalisation of this vein. In many cases the GSV was completely obliterated by the treatment and could not be identified on ultrasound.

The patient records were reviewed by the sponsor for completion of the study data points. After the data acquisition the investigators conducted a thorough audit of the raw data handling and storage methods, the data processing accuracy, and the presentation of the specific results. This was done twice, once after completion of 4-month follow-up (LK and FL), and again after completion of 2-year follow-up (RLK and FL). They reported that all of these were in order, and that the results accurately reflected the raw data received from the investigator sites. The sponsor, VNUS Medical Technologies, Inc. provided support limited to these functions, but did not interfere with the analysis of the data or the formulation of the conclusions.

Statistical methods

Student's *t*-test, and one-way ANOVA with Tukey-Kramer tests were used to analyse differences between the groups. The Mann-Whitney *U* test was utilised where appropriate. Differences were considered significant at the 95% level ($p < 0.05$). When comparisons were made between the score before treatment (baseline) and the score after treatment, repeated measures ANOVA was used. Alternatively, the absolute difference between the baseline score and the score after treatment for each individual patient was used (such as in Fig. 6). The Cochran-Mantel-Haenszel and Chi-square statistics were used for comparing the frequencies. Kaplan-Meier analysis and Long Rank test were used for analysis of time-series. All values presented as the mean and standard deviation (SD); the 95% confidence interval (CI) is also included where appropriate.

Results

The first 4 months of follow-up revealed an advantage of RFO in impact on quality of life, earlier return to usual level of physical activity (RTA) and earlier RTW. There were no major complications in either group. An important question at the time of the initial study was rate of the technical success of the Closure technique, mainly because it was a relatively new procedure. Immediate intra-operative success was reported in all but two cases.

Four months after Closure treatment four extremities demonstrated reflux in the proximal GSV. The lengths of refluxing segments were 4,22,28 and 30 cm. At 2-year follow-up one of these extremities had a closed GSV with no flow, another extremity exhibited the same length (4 cm) of open GSV segment but no reflux, and in the remaining two extremities the GSV remained open and incompetent.

In two patients we observed re-opening of an initially closed GSV lumen. In both cases the GSV remained closed at 4 months, but at 2-year follow-up a competent segment of GSV 23 cm long was found in one case, and a 34 cm long incompetent GSV segment was found in another case. In three S and L cases, open incompetent segments of saphenous vein were found in the immediate vicinity of original GSV location at the 2-year follow-up.

For the veins occluded by RFO, 51% of the GSV trunks showed a continuing decrease in diameter during the period of observation. Duplex ultrasonography showed that the external (adventitia-to adventitia) diameter of obliterated GSV decreased from a mean of 6.3 SD 1.4 mm 72 h after surgery to 2.9 SD 1.5 mm 2 years later ($p < 0.00001$; Fig. 2). An additional 41% of the GSVs became undetectable on

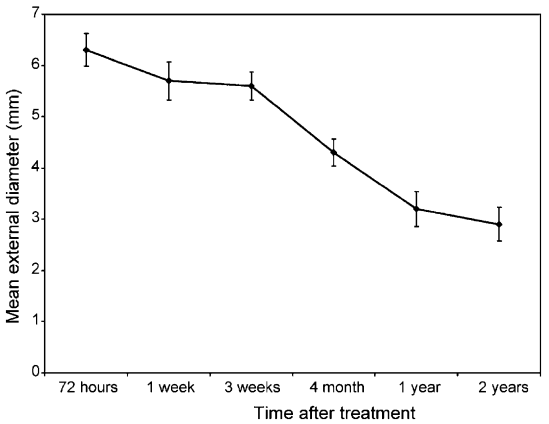

Figure 2 External (adventitia-to-adventitia) GSV diameter change in 20 RFO extremities in which GSV is still identifiable by ultrasound at 2-year follow-up.

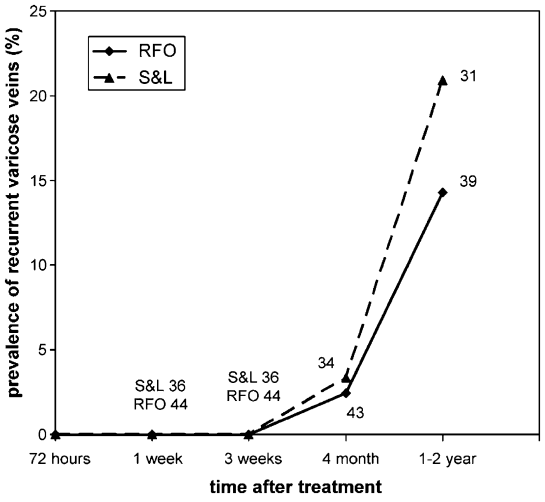

Figure 3 Cumulative prevalence of varicosities (Kaplan-Meier analysis).

ultrasound imaging at the 2-year follow up. Veins that decreased in size, but did not completely disappear were initially larger compared to those that became sonographically invisible. At 72 h after treatment their mean external diameters were 6.3 SD 1.4 mm and 4.3 SD 1.4 mm ($p = 0.0005$) respectively. The rate of diameter decrease was not significantly different in these groups (1.8 SD 0.9 mm/year and 2.2 SD 0.7 mm/year, $p = 0.085$). In three cases the GSV diameter did not change. Neovascularisation was observed in one RFO case and in four S and L cases.

Cumulative rates of recurrent varicose veins at combined 1 and 2 years follow-up were 14.3% for RFO and 20.9% for S and L ($p > 0.05$ Long Rank test, Fig. 3).

The clinical course of the disease was similar in both groups following treatment (Table 1). At the 2-year follow up, 12 patients (33%) after RFO and 8 patients (28%) after S and L had no sign of venous disease (CEAP clinical class C0). A statistically significant difference in VCSS score between the groups was observed at 72 h and 1 week after treatment (Fig. 4). This disappeared at all subsequent follow-up assessments.

Major differences between RFO and S and L groups at early follow-up were in time to return to usual levels of physical activity, time to RTW, and quality of life (QOL).[12] Although the difference in global QOL score was not significant at 3 weeks after treatment, it surprisingly reappeared at 1 year and remained significant at 2 years after treatment (Fig. 5). Pain was the only QOL dimension consistently reduced in the RFO group throughout all subsequent follow up both in absolute score and in change from the pre-treatment value (Fig. 6).

Discussion

Our earlier report showed advantage for RFO compared to S and L in the early follow-up period. These findings were consistent with observations of non-randomised studies.[15–17] The remaining question was the durability of the results. The fact that RFO violates two principles of a mainstream paradigm for surgical treatment of GSV reflux by leaving an open proximal segment of GSV and by leaving untouched the proximal GSV tributaries generated reasonable scepticism regarding long-term results.[21] Particular concern is the role of proximal tributaries in development of recurrent varicose veins.

Publications on the surgical treatment of GSV reflux provide the basis for questioning the role of proximal tributaries in development of recurrences. The majority of recurrent varicosities are located below the knee.[6] In a series of 264 limbs with recurrences 24.3 SD 12.5 year after surgery, Jiang et al. showed that the source of recurrence was confined to the groin in only 13.6%, and incompetent groin tributaries were present only in 12% of cases.[8] In a detailed ultrasound study Labropoulos et al. reported that in 65% of recurrences following stripping the GSV, the source of recurrence was other than in the groin. The clinical dynamics of primary chronic venous disease after surgical treatment have not been studied sufficiently to separate changes associated with surgery from those caused by natural history. Published reports suggest that new varicose veins can develop regardless of presence or absence of a refluxing GSV.[22]

In this study, the recurrence rate was numerically lower in the RFO group compared to the S and L group, but the difference did not reach the level of statistical significance due to insufficient numbers in our series. In three of five cases of recurrent veins in the RFO group a segment of thigh GSV was either not closed or re-opened. The likelihood of recurrence was 4.5 times higher in extremities with open GSV segments compared to extremities with a successful Closure treatment. This difference, however, did not reach the level of statistical significance (OR = 4.5, 95% CI = 0.7–28). Although our study was not powered to address these questions, the detected magnitude of differences between RFO and S and L groups and between extremities with permanently closed GSV and those with open GSV segments was substantial. This justifies further investigation of recurrent varicosity rates following both treatments, and with regard to status of the GSV.

Some experts have expressed the opinion that because the process of neovascularisation is associated with a groin incision, RFO may lead to a much less frequent neovascularisation compared to S and L.[23]

In our 2-year follow up of the EVOLVeS trial patients, neovascularisation was observed in four S and L patients and in one RFO patient. The numbers are too small to make a statement about the difference, but it is seen that neovascularisation can occur after RFO. It is important to mention here that the only case of neovascularisation after RFO occurred in a patient with initial technical failure, and the GSV remained open and incompetent during 2 years of observation.

Whether it is new vessels, or incompetent tributaries, they need to be connected to a remaining segment of GSV to cause clinical problems.[10] In all but five cases in this study, the lumen of the GSV was permanently closed at 2 years. Two of these five cases resulted from unsuccessful procedures (technical failures),[12] one was reported closed immediately after procedure but appeared open at 72 h after treatment, and in another two cases the GSV lumen re-opened during follow up (6%).

Although the issues of recurrence or neovascularisation are important, the EVOLVeS trial protocol was not designed

Table 1 Maximal clinical class ('C' of 'CEAP') before treatment and during follow-up.

	Maximal Clinical class	RFO (% of observed extremities)	S&L (% of observed extremities)	Pearson Chi-Square	*p*
Before treatment	C0	0	0	0.2	0.9
	C1	0	0		
	C2	81.8	77.8		
	C3	9.1	11.1		
	C4	9.1	11.1		
72 h	C0	54.5	66.7	1.7	0.6
	C1	25	13.9		
	C2	11.4	11.1		
	C3	0	0		
	C4	9.1	8.3		
1 week	C0	44.2	66.7	6.3	0.2
	C1	37.2	16.7		
	C2	11.6	8.3		
	C3	0	2.8		
	C4	7	5.6		
3 weeks	C0	54.5	52.8	0.1	0.99
	C1	27.3	30.6		
	C2	9.1	8.3		
	C3	0	0		
	C4	9.1	8.3		
4 months	C0	34.1	41.2	2.95	0.6
	C1	38.6	32.4		
	C2	18.2	20.6		
	C3	0	2.9		
	C4	9.1	2.9		
1 year	C0	28	15	5.8	0.2
	C1	56	40		
	C2	8	30		
	C3	0	5		
	C4	8	10		
2 years	C0	33.3	27.6	2.97	0.6
	C1	41.7	31		
	C2	22.2	31		
	C3	0	3.4		
	C4	2.8	6.9		

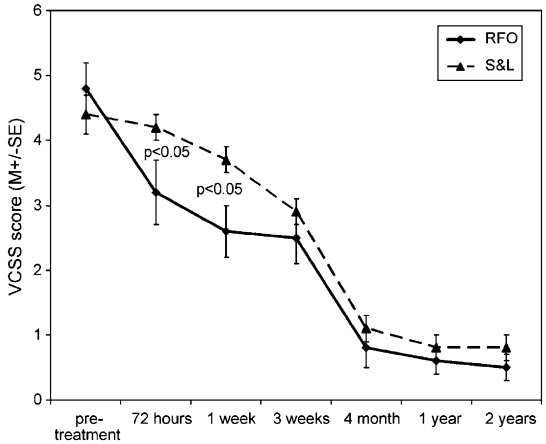

Figure 4 Changes in VCSS score. *P*-values are based on Mann-Whitney *U*-test.

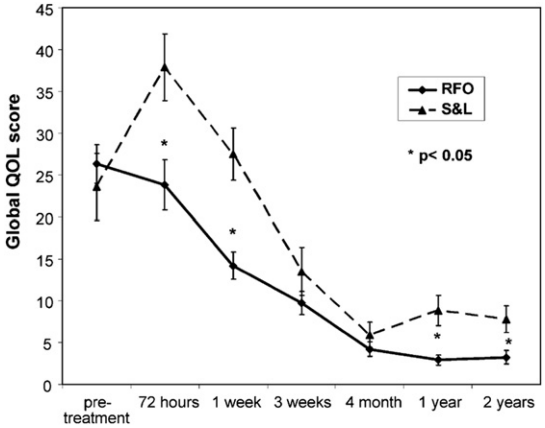

Figure 5 Global QOL score. *P*-values are based on Mann-Whitney *U*-test.

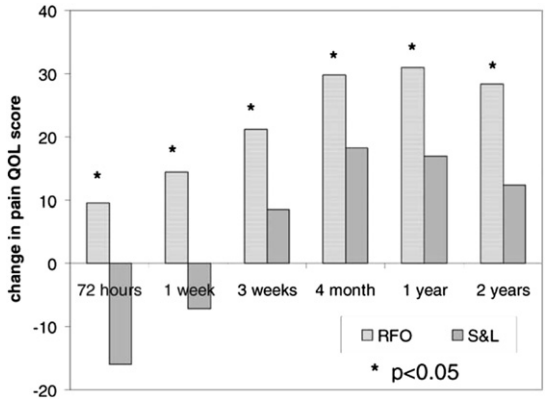

Figure 6 Change in pain QOL score compared to pre-treatment value. Negative values reflect decrease in quality of life. *P*-values are based on Mann-Whitney *U*-test.

to study them in-depth, but only to compare their rates in the two treatment groups. The results showed absence of significant differences between RFO and S and L patients at 2 years after treatment. It has been suggested that the pathological events leading to recurrence usually take place within 2 years and do not change thereafter.[7] In combination with our finding of progressive shrinkage and disappearance of the GSV trunk, this gives us confidence that our results can be expected to be maintained for a longer time than we have so far studied. As time progresses clinical changes are more likely to reflect the natural progression of disease than the difference in treatment techniques.

This study is also in line with published observations of changes in patients' quality of life after treatment. Major changes in QOL can be observed within 6 months after surgery and lesser change thereafter.[1]

One of the limitations of this study is that selection of the patients was based on indications for RFO that existed at the time of study initiation (2000). At the present time indications for RFO are much broader, which put the limits of generalisation of this study under question. However the same selection criteria were used for both RFO and S and L groups, so the results of comparison between the two treatments should be applicable to a broader population.

A 2-year clinical follow up of patients from the EVOLVeS trial showed that the results of radio- frequency obliteration were at least equal to those after high ligation and stripping of the great saphe- nous vein. Ultrasound follow-up demonstrated that in the vast majority of RFO patients the GSV remained permanently closed, and underwent progressive shrinkage to eventual sonographic disappearance. Recurrence and neovascularisation rates demonstrated trends toward being lower after RFO compared to S and L. Superior quality of life was demonstrated to be an early advantage of RFO, and this has persisted throughout the 2-year study period.

References

1 Mackenzie RK, Lee AJ, Paisley A, Burns P, Allan PL, Ruckley CV, et al. Patient, operative, and surgeon factors that influence the effect of superficial venous surgery on disease-specific quality of life. *J Vasc Surg* 2002;**36**(5):896—902.

2 Jawien A. The influence of environmental factors in chronic venous insufficiency. *Angiology* 2003;**54**(Suppl. 1):S19—31.

3 Jones L, Braithwaite BD, Selwyn D, Cooke S, Earnshaw JJ. Neovascularisation is the principal cause of varicose vein recurrence: results of a randomised trial of stripping the long saphenous vein. *Eur J Vasc Endovasc Surg* 1996;**12**:442—5.

4 Lacroix H, Nevelsteen A, Suy R. Invaginating versus classic stripping of the long saphenous vein: a randomized prospective study. *Acta Chir Belg* 1999;**99**:22—5.

5 Durkin MT, Turton EPL, Scott DJA, Berridge DC. A prospective randomised trial of PIN versus conventional stripping in varicose vein surgery. *Ann R Coll Surg Engl* 1999;**81**:171—4.

6 Campbell WB, Vijay kumar A, Collin TW, Allington KL, Michaels JA. Randomised and economic analysis of conservative and therapeutic interventions for varicose veins study. The outcome of varicose vein surgery at years: clinical findings, symptoms and patient satisfaction. *Ann R Coll Surg Engl* 2003; **85**(1):52—7.

7 Dwerryhouse S, Davies B, Harradine K, Earnshaw JJ. Stripping the long saphenous vein reduces the rate of reoperation for recurrent varicose veins: five-year results of a randomized trial. *J Vasc Surg* 1999;**29**(4):589—92.

8 Jiang P, van Rij AM, Christie R, Hill G, Solomon C, Thomson I. Recurrent varicose veins: patterns of reflux and clinical severity. *Cardiovasc Surg* 1999;**7**(3):332—9.

9 Labropoulos N, Touloupakis E, Giannoukas AD, Leon M, Katsamouris A, Nicolaides AN. Recurrent varicose veins: investigation of the pattern and extent of reflux with color flow duplex scanning. *Surgery* 1996;**119**(4):406—9.

10 Stonebridge PA, Chalmers N, Beggs I, Bradbury AW, Ruckley CV. Recurrent varicose veins: a varicographic analysis leading to a new practical classification. *Br J Surg* 1995;**82**(1):60—2.

11 Neglen P, Einarsson E, Eklof B. The functional long-term value of different types of treatment for saphenous vein incompetence. *J Cardiovasc Surg (Torino)* 1993;**34**(4):295—301.

12 Lurie F, Creton D, Eklof B, Kabnick LS, Kistner RL, Pichot O, et al. Prospective randomized study of endovenous radiofrequency obliteration (Closure procedure) versus ligation and stripping in a selected patient population (EVOLVeS study). *J Vasc Surg* 2003;**38**(2):207—14.

13 Rutgers PH, Kitslaar PJ. Randomized trial of stripping versus high ligation combined with sclerotherapy in the treatment of the incompetent greater saphenous vein. *Am J Surg* 1994;**168**: 311—5.

14 Bergan JJ. New technology and recurrent varicose veins. *Lancet* 1996;**348**:210—1.

15 Merchant RF, DePalma RG, Kabnick LS. Endovascular obliteration of saphenous reflux: a multicenter study. *J Vasc Surg* 2002; **35**:1190—6.

16 Pichot O, Kabnick LS, Creton D, Merchant RF, Schuller-Petrovic S, Chandler JG. Duplex ultrasound scan findings two years after great saphenous vein radiofrequency endovenous obliteration. *J Vasc Surg* 2004;**39**(1):189—95.

17 Weiss RA, Weiss MA. Controlled radiofrequency endovenous occlusion using a unique radiofrequency catheter under duplex guidance to eliminate saphenous varicose vein reflux: a 2-year follow-up. *Dermatol Surg* 2002;**28**(1):38—42.

18 Rutherford RB, Padberg Jr FT, Comerota AJ, Kistner RL, Meissner MH, Moneta GL. Venous severity scoring: an adjunct to venous outcome assessment. *J Vasc Surg* 2000;**31**: 1307—12.

19 Launois R, Reboul-Marty J, Henry B. Construction and validation of a quality of life questionnaire in chronic lower limb venous insufficiency (CIVIQ). *Qual Life Res* 1996;**5**:539—54.

20 Jantet G. Relief study: first consolidated European data. *Angiology* 2000;**51**:31—7.

21 Harris JE. Endovascular obliteration of saphenous vein reflux: a perspective. *J Vasc Surg* 2002;**35**:2192—4.
22 Makarova NP, Lurie F, Hmelniker SM. Does correction of superficial femoral vein valve change the course of varicose disease? *J Vasc Surg* 2001;**33**:361—8.
23 Jones L, Braithwaite BD, Selwyn D, Cooke S, Earnshaw JJ. Neovascularisation is the principal cause of varicose vein recurrence: results of a randomized trial of stripping the long saphenous vein. *Eur J Vasc Endovasc Surg* 1996;**12**(4): 442—5.